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EPIGENETICS

Fatherly histone influences

Environmentally induced traits can be transmitted epigenetically from parents to their offspring, and some can persist through multiple generations. However, little is known about the epigenetic mechanisms underlying paternal transmission. Now, Siklenka *et al.* show that transgenerational epigenetic inheritance of developmental abnormalities in mice can be triggered by abnormal histone demethylase activity during spermatogenesis.

The authors generated transgenic mice that overexpress the human histone demethylase KDM1A in testicular germ cells during spermatogenesis. Male transgenic mice were bred with wild-type females, resulting in male heterozygous transgenic (TG) offspring and nontransgenic (nonTG) offspring. The TG and nonTG littermates were bred with wild-type females for several generations, and the survival and fitness of pups from each generation were assessed. Litters sired by TG or nonTG fathers exhibited reduced survival and an increased frequency of developmental abnormalities compared with controls, and mortality increased with each generation of exposure to the transgene in TG offspring. Interestingly, in nonTG mice (which do not express the *KDM1A* transgene but are descended from mice that do), the aberrant phenotypes persisted for two generations following transgene exposure, strongly suggesting a transgenerational epigenetic mechanism of inheritance.

To examine the chromatin state of parental spermatozoa, the authors used chromatin immunoprecipitation followed by sequencing (ChIP–seq) analysis to profile the epigenetic mark histone H3 lysine 4 dimethylation (H3K4me2), which is targeted by KDM1A, in the genomes of sperm from TG males and their nonTG siblings. This analysis revealed a reduction in the level of H3K4me2 enrichment in sperm from TG mice but not in sperm from nonTG mice, indicating that the phenotypic abnormalities observed in nonTG-sired offspring are not directly linked to reduced levels of H3K4me2 in sperm. Further experiments showed no difference in the genome-wide levels of DNA methylation at CpG islands in sperm from TG and nonTG mice compared with controls, ruling out altered DNA methylation as a mechanism for transmission.

To assess RNA as a potential mediator of aberrant phenotype transmission, the authors used microarray analysis to compare the RNA profiles of sperm and identified more than 560 transcripts that were differentially regulated in both TG and nonTG sperm compared with controls. Interestingly, 41 of these transcripts were associated with genes that had reduced levels of H3K4me2 at their promoters in TG sperm. The authors suggest the possibility that the observed transmission of developmental defects might be mediated by RNAs transferred to the embryo by TG and nonTG sperm.

Finally, to assess a potential link between altered histone methylation in sperm and gene expression in embryos, the authors carried out microarray expression analysis of two-cell embryos that were sired by TG, nonTG or control mice. More than 100 of the genes that had reduced histone methylation in TG sperm were differentially regulated in embryos sired by TG or nonTG mice compared with controls and, notably, some of these genes could be linked to the developmental abnormalities displayed by the offspring of TG and nonTG mice.

These studies show that altering histone methylation in developing sperm cells can induce developmental abnormalities in offspring that can be inherited through several generations, even in the absence of transgene expression, and are associated with altered RNA profiles in sperm and embryos. The authors suggest that environmentally or genetically induced alterations in histone methylation are potential causes of birth defects that are linked to the father.

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ORIGINAL RESEARCH PAPER Siklenka, K. *et al.* Disruption of histone methylation in developing sperm impairs offspring health transgenerationally. *Science* http://dx.doi.org/10.1126/science.aab2006 (2015)